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Clinical and histological determinants of uterine leiomyoma recurrence following myomectomy

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Abstract

Aim: Uterine leiomyomas are frequent benign tumors of the female genital system, and a substantial proportion of them recur following therapy. In this study, the clinical and histological characteristics that influence leiomyoma recurrence in women who have undergone surgical therapy for uterine leiomyoma were evaluated.

Material and Methods: Patients who underwent myomectomy for uterine leiomyoma at a tertiary center between 2012 and 2021 were retrospectively analyzed. Demographic characteristics of the patients, clinical results, surgical techniques, and data on leiomyoma recurrence were investigated and evaluated. Recurrence was defined as the appearance of a new leiomyoma that was 1 centimeter or larger in size at transvaginal ultrasonography, which was performed at least 6 months following myomectomy.

Results: The study comprised 594 patients with a mean age of 36.3±5.5 (16–53) years and a mean follow-up duration of 23 (6–72) months. Recurrence was detected in 118 (19.9%) of the patients. Estimated recurrence times were found to be 70.5±2.5 months, and the 1-year period without recurrence was 96.4%. The number of patients who were reoperated due to recurrence was 48 (8%). It was determined that the recurrence rate was higher in submucosal leiomyomas and lower in subserous leiomyomas ($p = 0.002$). In addition, cellular myomas were found to have a higher risk of recurrence ($p = 0.009$). In patients who had pregnancy or delivery after myomectomy, recurrence rates were significantly lower ($p = 0.0001$). Laparoscopic or laparotomic surgery was not shown to be statistically associated with recurrence ($p = 0.326$).

Discussion: Myoma recurrence risk is influenced by the myoma's location and histological characteristics. The recurrence rate appears to be similar after laparoscopic and laparotomic surgery. Follow-up in terms of recurrence risk may be guided by a careful evaluation of the clinical findings of the patients and an extensive pathological examination.

Keywords

Cellular Myoma, Laparoscopic Myomectomy, Myoma Uteri, Recurrence, Uterine Leiomyoma

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Introduction

Uterine leiomyomas (UL) are the most prevalent benign tumors of the female reproductive tract [1]. Although more than half of the women with uterine leiomyomas are asymptomatic [2], uterine leiomyomas frequently present with menorrhagia, pelvic pain, a pelvic mass, and infertility, which require treatment in many women of reproductive age [1].

Medical and surgical therapy options are available, while many patients who have undergone a myomectomy have a recurrence during later follow-ups [3]. Compared to surgical treatment, medical treatment is associated with a higher incidence of UL recurrence [4]. Predicting the probability of recurrence risk is important for treatment choice. Surgery for symptomatic leiomyomas includes hysterectomy, myomectomy, and uterine artery embolization. The patient's age, fertility goals, leiomyoma size and number, and risk of recurrence determine the treatment.

The association between clinical parameters such as the number and size of leiomyomas, type of surgical treatment, and parity after myomectomy and leiomyoma recurrence has been explored in the current literature. However, the effect of these factors on the risk of recurrence is not well understood. Studies on histological variables that influence recurrence are even rarer [5]. Currently, gynecologists assess the risk of UL recurrence and make a subjective determination based on their own personal experience.

This study aims to analyze the clinical and histological risk factors of patients with leiomyoma recurrence during follow-up after myomectomy, as well as to identify the objective risk variables associated with recurrence.

Material and Methods

Data of the patients who were diagnosed with uterine leiomyoma and underwent myomectomy at the Gynecology and Obstetrics Clinic of a tertiary center between 2012 and 2021 were analyzed retrospectively through the hospital registry system.

Patients' demographic information, including age, body mass index (BMI), gravida, and parity, were recorded. Complaints at hospital admission, clinical characteristics of detected leiomyomas, including number, location, size, type of surgical procedure performed, need for medical treatment or re-surgery in the follow-up of patients after treatment, and pregnancy and delivery histories following myomectomy were recorded.

Myomectomy was performed either by laparoscopy, laparotomy, or hysteroscopy, taking into account the number, location, and size of the myomas, clinical suspicion of malignancy, and age, BMI, and desire for fertility of the patient. In laparoscopic myomectomies, especially in recent years, myomas are taken out of the abdomen in a safe-bag.

This study included typical leiomyoma, mitotic active leiomyoma, cellular leiomyoma, epithelioid leiomyoma, and leiomyomas with bizarre nuclei (atypical leiomyomas) regarding histopathological assessment. In addition, the existence of hyaline degeneration, ischemic necrosis, and myxoid alterations in myoma nodules were considered during evaluation. Recurrence was defined as the appearance of a new leiomyoma measuring 1 cm or greater on transvaginal ultrasonography after a period of at least 6 months following myomectomy [6].

Data analysis was performed using the SPSS 25.0 package program. Categorical measurements were summarized using numbers and percentages, whereas continuous measurements were summarized using mean and standard deviation (median and range where appropriate). Statistical comparisons were conducted between two subgroups with and without myoma recurrence. Distributions were controlled and the Student's t test was used for variables with a parametric distribution and the Mann-Whitney U test was used for variables with a nonparametric distribution when comparing continuous measurements. The Chi-Square or Fisher Exact test was utilized to analyze the categorical variables between the groups. All tests were considered statistically significant if $P< 0.05$.

Ethical Approval

This research was approved by the Baskent University Institutional Review Board (Date: 2022-03-15, No: KA22/104)

Results

In our clinic, a total of 1,462 myomectomies were performed between 2012 and 2021. Our study comprised patients who were followed a minimum of once, at least six months following myomectomy. Thus, the study included 594 patients with a mean age of 36.3±5.5 years and a mean follow-up duration of 23 (6-72) months. The study included 594 patients with a mean age of 36.3±5.5 years and a mean follow-up duration of 23 (6–72) months. There was recurrence in 118 (19.9%) of the 594 patients who were included in the study. Of those 118 patients, 48 (8%) required additional surgery to treat the recurrence, and the estimated time to recurrence was 70.5±2.5 months. There was no difference in terms of age at diagnosis, gravida, BMI, number of leiomyomas, or leiomyoma diameter between the groups with and without recurrence. The median leiomyoma diameter was 6 cm (1 to 25), and the median recurrent leiomyoma diameter was 3 cm (1–11).

It was found that 11 (0.001%) of the patients underwent hysteroscopy, 374 (62.9%) underwent laparoscopy, and 202 (34%) underwent myomectomy via laparotomy. Of those who underwent laparoscopy, 63 (16.8%) utilized a safe-bag. In terms of recurrence, there was no statistically significant difference between patients undergoing laparoscopy and laparotomy; however, statistically significant recurrence was found in patients who underwent hysteroscopic myomectomy ($p = 0.02$). It was also seen that removing the leiomyoma via a safe-bag in laparoscopic surgery did not significantly affect the risk of recurrence ($p = 0.592$) (Table 1).

At the time of the initial diagnosis of patients who had recurrence, 40.3% presented with abnormal uterine bleeding, 23.5% with pelvic pain, and 16.8% with infertility symptoms. On the other hand, in the group who did not experience recurrence after surgery, 35% of patients initially presented to the gynecologist with infertility symptoms, while in 25.1% of patients, leiomyomas were identified incidentally in asymptomatic patients ($p = 0.0001$).

As per location, 21 (3.5%) of patients had submucous leiomyomas, 317 (53.8%) had intramural leiomyomas, 99 (16.8%) had subserous leiomyomas, and 152 (25.8%) had mixed-type leiomyomas. The probability of recurrence for

Table 1. Comparison of clinical features of patients with and without myoma recurrence

	Without recurrence	With recurrence	p
	N(%)	N(%)	
Parity			
Multiparity	156 (33.1)	45 (38.1)	0.329
Nulliparity	316 (66.9)	73 (61.9)	
Surgical approaches			
Laparotomic myomectomy	159 (33.4)	43 (36.4)	0.020
Laparoscopic myomectomy	307 (64.4)	67 (56.8)	
Histeroscopic myomectomy	5 (1.1)	6 (5.1)	
Removal of vaginal leiomyoma	5 (1.1)	2 (1.7)	
Obezitiy			
BMI < 30	134 (72.0)	42 (84.0)	0.100
BMI ³ 30	52 (28.0)	8 (16.0)	
Symptoms			
Asymptomatic	120 (25.1)	17 (14.3)	0.0001
Vajinal bleeding	99 (20.8)	48 (40.3)	
Pelvic pain	64 (13.4)	28 (23.5)	
Compression findings	8 (1.7)	3 (2.5)	
Infertility	171 (35.0)	19(16.8)	
Palpable mass	14 (2.9)	3 (2.5)	
Multiple/single			
Multiple	248 (52.2)	56 (47.5)	1.00
Single	227 (47.8)	62 (52.0)	
Myoma location			
Submucosal	13 (2.7)	8 (6.9)	0.002
Intramural	244 (51.6)	73 (62.9)	
Subserous	90 (19.0)	9 (7.8)	
Mixed-type	126 (26.6)	26 (22.4)	
Laparoscopic myomectomy with safe-bag			
No	257 (83.7)	55 (80.9)	0.592
Yes	50 (16.3)	13 (19.1)	
Postoperative pregnancy			
No	311 (65.6)	104 (89.0)	0.0001
Yes	163 (34.4)	13 (11.0)	
Postoperative delivery			
No	347 (76.4)	110 (94.0)	0.0001
Yes	107 (23.6)	7 (6.0)	
Postoperative medical treatment			
No	458 (96.6)	106 (92.2)	0.152
Yes	16 (3.4)	8 (7.8)	

submucous fibroids was significantly higher (p = 0.001). Pregnancy or delivery following myomectomy were found to decrease recurrence substantially (p = 0.0001). Although medical treatments such as GnRH (Gonadotropin releasing hormone) analogs, intrauterine devices with levonorgestrel, or oral contraceptives were utilized in 8% of patients during postoperative follow-up, no significant change in recurrence rates was identified (Table 1).

Histopathologically, 482 patients had typical leiomyomas, 49 had mitotic active leiomyomas, 3 had epithelioid leiomyomas, 51 had cellular leiomyomas, and 9 patients had leiomyomas with bizarre nuclei. Leiomyomas with hyaline degeneration were found in 48 patients, ischemic necrosis was seen in 67 patients, and myxoid differentiation in 16 patients. The incidence of recurrence of cellular leiomyomas was reported to be considerably higher (p = 0.009), while the existence of

Table 2. Pathological variables of leiomyomas at patients with and without recurrence

	Without recurrence	With recurrence	p
	N (%)	N (%)	
Mitotic active leiomyoma			
No	440 (92.4)	105 (89.0)	0.260
Yes	36 (7.6)	13 (11.0)	
Epithelioid leiomyoma			
No	474 (99.6)	117 (99.2)	0.486
Yes	2 (0.4)	1 (0.8)	
Cellular leiomyoma			
No	443 (93.1)	100 (84.9)	0.009
Yes	33 (6.9)	18 (15.1)	
Atypical leiomyomas			
No	469 (98.6)	116 (98.3)	0.695
Yes	7 (1.4)	2 (1.7)	
Hyaline degeneration			
No	434 (91.2)	112 (95.0)	0.256
Yes	42 (8.8)	6 (5.0)	
Ischemic necrosis			
No	417 (87.6)	110 (93.2)	0.103
Yes	59 (12.4)	8 (6.8)	
Myxoid alterations			
No	462 (97.1)	116 (98.3)	0.750
Yes	14 (2.9)	2 (1.7)	

Table 3. Periods without recurrence according to myoma location and cellular histopathology

	Estimate Meana	Std. Error	95% Confidence Interval		1.year %	3.year %	5.year %	p
			Lower Bound	Upper Bound				
Period without recurrence (month)	70.5	2.5	65.5	75.4	96.4	82.0	63.8	-
Myoma location								
Submucous	37.7	6.9	24.Nis	51.2	72.8	54.6	27.Mar	0.0001
Intramural	67.3	3.3	60.8	73.5	96.6	78.3	55.3	
Subserous	82.4	3.3	76.0	88.9	96.8	89.2	68.9	
Mixed-type	69.7	4.3	61.2	78.3	96.1	85.3	69.5	
Cellular leiomyoma								
No	72.4	2.7	67.3	77.7	96.8	82.6	67.6	0.001
Yes	50.0	4.6	40.9	59.1	91.7	70.6	31.May	

mitotic active leiomyoma, epithelioid differentiation, atypia, hyaline degeneration, myxoid alteration, or ischemic necrosis did not significantly affect the risk of recurrence ($p > 0.05$) (Table 2).

A Kaplan-Meier analysis was used to determine the recurrence time of the participants. The estimated recurrence time for the patients was 70.5±2.5 months, and a 1-year period without recurrence was seen in 96.4% of the patients (Table 4). Myoma location significantly affected recurrence. The recurrence time was statistically substantially shorter in patients with submucous myoma, as indicated by the Kaplan-Meier method. The 3-year period without recurrence was determined to be 54.6% for submucous myomas, 78.3% for intramural myomas, 89.2% for subserous myomas, and 85.3% for mixed myomas. The 3-year period without recurrence for patients without cellular myoma was 82.6%, compared to 70.6% for patients having myoma with cellular characteristics ($p = 0.001$) (Table 3). In terms of variables such as age at diagnosis, follow-up period, gravida, parity, BMI, largest myoma diameter, recurrence diameter, and recurrence time, a statistically significant difference was not found between patients who had recurred and undergone reoperation and patients who had recurred but had not undergone surgery after their initial relapse ($p > 0.05$).

Discussion

In this retrospective, single-center analysis of 594 women who underwent myomectomy at our clinic, the probability of recurrence of cellular myomas was found to be greater ($p=0.009$), and less recurrence was reported in patients who had pregnancy or delivery following myomectomy ($p=0.0001$). In addition, a statistically significant relation between myoma location and recurrence was reported. Submucous myomas were shown to have considerably shorter recurrence periods. Recurrence was observed to be more prevalent following hysteroscopic myomectomy for submucous myomas ($p=0.002$) Laparoscopic or laparotomic surgery was not significantly associated with recurrence ($p=0.326$). The use of a safe-bag did not have a statistically significant effect on recurrence in laparoscopic myomectomy patients ($p=0.592$).

Myomectomy with laparotomy was generally anticipated to have a lower recurrence rate than laparoscopic myomectomy because gynecologists could remove as much of the visible and palpable leiomyomas as possible during laparotomy [6, 7]. However, there are studies indicating that the incidence of UL recurrence after myomectomy is comparable between laparotomy and laparoscopy [6, 8, 9]. In the study of Kotani et al., recurrence following laparotomy and laparoscopic myomectomy were compared, and myomectomy via laparoscopy was found to be associated with an increased risk of recurrence. A lower postoperative recurrence rate is believed to be due to less remaining fibroid mass after myomectomy through laparotomy [7]. According to research published in 2019 by Ming et al., the incidence of UL recurrence was similar between laparoscopy and laparotomy in patients with ≤ 5 leiomyomas. When there were > 5 leiomyomas, the recurrence rate of myomectomy performed by laparoscopy was significantly greater. It was demonstrated that the reoperation rate of uterine leiomyomas was comparable between laparoscopy and laparotomy in women between the ages of 18 and 44 who had ≤ 3 leiomyomas [10]. In our study, we found no difference in recurrence between laparotomic and laparoscopic myomectomy. On the other hand, we concluded that submucous myomas and thereby hysteroscopic myomas have a significant recurrence rate. Since submucous leiomyomas cause more symptoms, such as irregular uterine bleeding and infertility, when compared to leiomyomas at other locations, patients with submucous leiomyomas may virtually seem to have a considerably greater recurrence rate due to frequent follow-up [7].

Removal of the material in a safe-bag during laparoscopic myomectomy appears to be a safe and feasible operation for lowering the danger of malignant cell and tissue spread [11]. In a few retrospective investigations, it was demonstrated that during laparoscopic myomectomy, morcellation without the use of a safe-bag was associated with an elevated recurrence rate and decreased long-term survival rate in cases of malignancy [12, 13]. There is a large body of literature regarding the utilization of safe-bags on sarcoma extension in patients who were first diagnosed with leiomyomas but were later discovered to have leiomyosarcoma on pathology and parasitic leiomyomas [11-13]. However, there is little research on local leiomyoma recurrence. In our study, it was found that removing the leiomyoma material via a safe-bag had no effect on recurrence. However, this result may be due to the small sample size. In recent years, safe-bags have been utilized in all laparoscopic myomectomies performed at our clinic in order to avoid the potential risk of cancerous spread.

According to Kotani's study [7], the absence of pregnancy after myomectomy considerably raised the recurrence rate. Progesterone receptor modulators have been proven to diminish the size of UL and the intensity of associated symptoms [14-16]. In a study, the anti-progestational steroid mifepristone 5 mg daily for three months lowered UL volume considerably [17]. It has been questioned whether pregnancy-related hormonal changes have comparable effects on UL. Pregnancy or delivery following myomectomy also decreased the incidence of UL recurrence in our study sample, corroborating the findings of earlier observational studies [18, 19].

Cellular leiomyomas (CL) are fibroids that resemble leiomyomas and leiomyosarcomas. Taran et al. examined CL recurrence and clinical and pathological features. CLs were linked to the largest uterine mass diameter, menometrorrhagia, fewer leiomyomas, no endometriosis or adenomyosis, and a rapidly expanding leiomyoma as a surgical indication [20]. In terms of recurrence rates, the results of the study by Rathmound et al analyzing the clinical and histological characteristics of cellular myomas were comparable to those reported in Taran et al's biggest CL series to date [20, 21]. This is also consistent with the reports demonstrating that a uterus with a single myomatous lesion grows more rapidly than one with numerous masses [22]. Additional research is required to determine whether the rapid growth phenotype is related to all single leiomyomas or only those with cellular histology abnormalities. In our study, it was found that the recurrence time of the cellular fibroids was statistically shorter. Furthermore, the rapid growth pattern of CL is demonstrated in consistency with the current literature. Although CL recurrence rates were comparable to UL recurrence

rates in the report of Rothmund et al. [20], our analysis revealed a higher recurrence rate for CL.

The literature indicates that abnormal uterine bleeding (AUB) is the most common indication for hysteroscopic myomectomy, with percentages ranging from 60% to 84% [23]. In our study, 7 (63%) of 11 patients who underwent hysteroscopic myomectomy consulted a gynecologist for AUB and 4 (36%) for infertility, which is consistent with the literature. The success rates for hysteroscopic myomectomy described in the literature represent the myomectomy outcomes for all submucous myomas (Types 0, 1 and 2). Fibroids of type 2, which are technically more challenging to remove, are believed to have a lower success rate. Reoperation rates for hysteroscopic myomectomies range from 10% to 35% [24]. This rate can approach 50% in type 2 leiomyomas [25]. A second session for the total removal of the myoma is usually planned in the following months, which is not considered as a recurrence. However, even after the total removal of the myoma, the existence of new myoma nuclei may be encountered. In our study, recurrence was seen in 6 (54%) of 11 patients who had undergone hysteroscopic myomectomy, and the number of reoperations was 3, which was consistent with the literature [24-25].

The most significant limitation of this study is its retrospective design. The number of patients with submucous myomas and hysteroscopic operations in this study was apparently lower, though notable outcomes were obtained even in this group. Additionally, data from a particular institution may not be indicative of the community as a whole. Moreover, the outcome would be more generalizable if all patients who underwent myomectomy had undergone routine follow-up. A longer duration of follow-up may increase the probability of detecting a recurrence.

In conclusion, in this study evaluating the factors influencing UL recurrence in women who had myomectomy and were diagnosed with UL recurrence, it was found that patients with relapse were admitted to the hospital more frequently with symptoms of vaginal bleeding and pain at the initial presentation. The presentation type of the myoma was determined to be a risk factor for recurrence. This study also demonstrated that the recurrence rates following laparotomic and laparoscopic myomectomy were comparable, adding to a debate that is still unclear in the literature. The recurrence times of submucous leiomyomas and cellular leiomyomas were observed to be statistically significantly shorter. Patients who had pregnancy or delivery after myomectomy were found to have significantly lower rates of recurrence. The risk of recurrence, therefore, can be guided by a thorough evaluation of the clinical findings of the patients and an extensive pathological examination. However, prospective studies with larger populations are required for a comprehensive analysis of the clinical and histopathological factors affecting recurrence following myomectomy.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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